Remarks

Upon entry of the foregoing amendment, claims 1-9 are pending in the application, with claim 1 being the independent claim.

The specification has been amended to include sequence identifiers for Figures 1A-1C. It is believed that this change introduces no new matter, and its entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and further request that they be withdrawn.

Objection to the Drawings/Specification

The Application was objected to for not including sequence identifiers in the drawing or in the Brief Description of the Figures.

The specification has been amended in the Brief Description of the Figures to include sequence identifiers for Figures 1A-1C. Applicants believe the Application is now in compliance with MPEP 2422.02. Accordingly, withdrawal of the objection is respectfully requested.

Obviousness-type Double Patenting Rejection

Claims 1-9 were rejected were rejected under the judicially-created doctrine of obviousness-type double patenting over the claims of U.S. Patent No. 6,759,519.

Applicants submit herewith a Terminal Disclaimer to Obviate a Double Patenting Rejection Over a "Prior" Patent ("Terminal Disclaimer"). As the present Application and

U.S. Patent No. 6,759,519 are commonly owned, it is believed that the Terminal Disclaimer obviates this rejection. According, withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. § 101

Claims 1-9 were rejected under 35 U.S.C. § 101 because they allegedly "are drawn to an invention with no apparent or disclosed specific and substantial credible utility." (Paper No. 20051125, page 3.) The Examiner acknowledged that the specification discloses the use of HDGNR10 (now known in the art as CCR5) molecules of the invention for treating a number of diseases (*id.* at pages 3-4), but stated that no evidence or sound scientific reasoning has been presented to support these uses (*id.* at page 4), and that the number of asserted uses is not credible (*id.*).

As discussed below, Applicants have asserted at least one specific, substantial credible utility and the invention therefore fulfills the requirements of 35 U.S.C. § 101.

A. The Specification Discloses at least One Credible, Substantial, Specific Utility.

The specification discloses that inhibitors of HDGNR10 (CCR5) may be used to treat rheumatoid arthritis, among other diseases and conditions. Specification, ¶ [0018]; *see also* ¶ [0094]. Inhibitors of HDGNR10 (CCR5) include antibodies and soluble forms of the receptor. *See* specification, ¶¶ [0088] and [0092].

Contrary to what the Examiner suggests, Applicants need not *confirm* any asserted utility. Applicants need only to *assert* one specific utility of the claimed invention; all aspects of the claimed utility are not required to be proven. *See Nelson v.*

Bowler, 626 F.2d 853, 856-57 (CPPA 1980). An assertion of utility need only be "reasonably predictive" (as opposed to "reasonably confirmed"); it need not be a "statistical certainty." *See, e.g.*, *Rey-Bellet v. Englehardt*, 493 F.2d 1380 (CPPA 1974); MPEP § 2107.01; *Nelson v. Bowler*, 626 F.2d 853, 856-57 (CPPA 1980). Nevertheless, Applicants provide below several publications that confirm HDGNR10's usefulness in treating rheumatoid arthritis.

B. Post-Filing Date Art Confirms the Utility of HDGNR10 in Rheumatoid Arthritis.

The Examiner's attention is respectfully directed to several post-filing date publications that have implicated HDGNR10 (CCR5) in rheumatoid arthritis. See, e.g.,Gomez-Reino, J.J. et al., *Arthritis Rheum. 42*:989-92 (1999); Mack, M., et al. *Arthritis Rheum. 42*:981-8 (1999); Suzuki, N. et al., *Intl. Immunology 11*:553-559 (1999); and Zang, Y.C.Q. et al., *Brain 123*:1872-1884 (2000) (IDS Documents AR9, AR13, ARS19, and AR21, respectively). For example, Suzuki et al. found that T cells expressing CCR5 selectively accumulate in the inflamed joints of patients with rheumatoid arthritis. Moreover, just as the original specification states, e.g., at page 5, the authors of these three publications indicate that a protein of the invention would be a good target for treating rheumatoid arthritis. See, e.g., Gomez-Reino et al., at 991 ("*blocking of CCR5 with specific monoclonal antibodies and synthetic peptides*, or by other means, could potentially be a promising *therapeutic approach*." (emphasis added)).

Thus, these publications by others confirm the use of HDGNR10 in the treatment of rheumatoid arthritis.[1]

Moreover, Applicants respectfully direct the Examiner's attention to an additional post-filing date publication by others: Brühl, H. et al., *J. Immunology 166*:2420-26 (2001) (IDS Document AR3). Brühl et al. disclose that "in a variety of chronic inflammatory diseases, an impressive accumulation of CCR5-positive T cells and macrophages is found at the site of inflammation. . . . Therefore, CCR5 appears to be an excellent marker to identify leukocytes that are involved in chronic inflammation." Brühl et al. at 2420. The authors further disclose that:

> In chronic inflammation such as *rheumatoid arthritis* . . . a clear predominance of T cells and monocytes expressing the chemokine receptor CCR5 is found within the affected tissues. . . . In contrast, in the peripheral blood only a minority of T cells and monocytes express CCR5.

Brühl et al. at 2424 (emphasis added). Brühl et al. further state that:

> [W]e describe a bispecific single-chain Ab that simultaneously binds to CCR5 and CD3 and thereby redirects T effector cells against CCR5-positive target cells.

Brühl et al. at 2424-2425 (*see also* figures 5 and 6).[2] The authors conclude by saying, "[s]pecific depletion of chemokine receptor-positive cells can be achieved with bispecific

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[1] The present specification states that antibodies of the invention include single chain antibodies. *See* specification, ¶ [0126]. Methods of making bispecific single chain antibodies were known when the present application was filed. *See, e.g.*, references 19, 22, and 23 (dated 1993 or 1994) cited in Brühl et al.

Abs . . . and may represent a new strategy in the treatment of chronic inflammatory diseases." *Id.* at 2425.

The disclosures in Brühl et al., Gomez-Reino et al., Mack et al. and Suzuki et al., confirm the credibility of using HDGNR10 (CCR5) antibodies and soluble fragments to treat rheumatoid arthritis. *See* specification, ¶¶ [0088] and [0092].

C. Assertion of <u>One</u> Credible Utility is Sufficient Under 35 U.S.C. § 101.

The Federal Circuit has articulated a standard for utility:

> The threshold of utility is not high: An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 (1996); *Brooktree Corp. v. Advanced Micro Devices*, Inc., 977 F.2d 1555, 1571 (Fed. Cir. 1992) ("To violate § 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is capable of serving any beneficial end").

Juicy Whip, Inc. v. Orange Bang Inc., 185 F.3d 1364, 1366, 51 U.S.P.Q.2d 1700, 1702 (Fed. Cir. 1999).

Further, Applicants "need only make ***one*** credible assertion of specific utility for the claimed invention to satisfy 35 U.S.C. 101 and 35 U.S.C. 112; ***additional statements of utility, even if not 'credible,' do not render the claimed invention lacking in utility.***" MPEP § 2107.02 at 2100-37 (emphasis added); *see also In re Gottlieb*, 140 USPQ 665, 668 (CCPA 1964) ("Having found that the antibiotic is useful for some purpose, it becomes unnecessary to decide whether it is in fact useful for the other purposes 'indicated' in the specification as possibly useful."). In fact, the Federal Circuit has indicated that

> [t]o meet the utility requirement, the Supreme Court has held that a new product or process must be shown to be "operable" - that is, it must be "capable of being used to effect the object proposed." Our cases have not, however, interpreted this language . . . to mean that a patented device must accomplish *all* objectives stated in the specification. On the contrary, "[w]hen a properly claimed invention meets at least one stated objective, utility under § 101 is clearly shown."

Carl Zeiss Stiftung v. Renishaw plc, 20 USPQ2d 1094, 1100 (Fed. Cir. 1991) (citations omitted) (quoting *Raytheon Co. v. Roper Corp.*, 220 USPQ 592, 598 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 (1984)).

Therefore, even assuming, *arguendo*, that the remainder of the asserted uses lack credibility, the assertion regarding rheumatoid arthritis is sufficient to fulfill the requirement under 35 U.S.C § 101.[3] Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 101 be reconsidered and withdrawn.

Rejections Under 35 U.S.C. § 112 – Enablement

Claims 1-9 were rejected under 35 U.S.C. § 112, as the specification allegedly fails to teach how to use the invention, for the reasons given above in connection with the utility rejection.

For the reasons discussed above in reply to the utility rejection, Applicants assert that the claimed invention is supported by a specific, substantial and credible utility. Therefore, since the claimed invention complies with the utility requirement of 35 U.S.C. § 101, the rejection under 35 U.S.C. § 112, first paragraph, based on the alleged lack of utility of the claimed invention, should be withdrawn.

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[3] Applicants reserve the right to establish the credibility of other asserted uses.

Claim 8 was rejected under 35 U.S.C. § 112, as the specification allegedly fails to teach how to use the claimed antagonist antibody. Applicants' respectfully disagree.

Applicants wish to point out to the Examiner that it is irrelevant to enablement whether or not the ligand for HDGNR10 was disclosed. Contrary to what the Examiner suggests, an artisan of ordinary skill need not know the identity of a receptor's ligand in order to make antagonistic antibodies against that receptor. It was well known to one of ordinary skill in the art at the time of filing that one could utilize an antibody to antagonize a receptor's function absent knowledge of the ligand. (E.g., Lin et al., *Transplantation 59*:1162-71 (April 1995) (copy of abstract enclosed) (anti-CD2 antibody down-modulates CD2 expression on the cell surface.)) Thus, it is clear that knowledge of the ligand for a receptor is not required to identify antagonist antibodies to that receptor.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112 be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will

expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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1: Transplantation. 1995 Apr 27;59(8):1162-71. Related Articles, Links

Anti-CD2 monoclonal antibody-induced receptor changes: down modulation of cell surface CD2.

Lin J, Yon RW, Chavin KD, Qin L, Woodward J, Ding Y, Yagita H, Bromberg JS.

Department of Microbiology, Medical University of South Carolina, Charleston 29425, USA.

Anti-CD2 mAbs suppress T cell immunity and prolong allograft survival in vivo while inducing the down-modulation of CD2 expression. Manipulation of cell surface molecules may be important in inducing tolerance, so down-modulation of CD2 expression on T cells by anti-CD2 mAbs was further defined with an in vitro model. The anti-CD2 mAb 12-15 caused CD2 expression on purified splenic T cells to decrease from 83.4 to 22.7% total positive cells while CD3, CD4, and CD8 expression remained unchanged. The expression of other adhesion molecules, LFA-1 alpha (CD11a), LFA-1 beta (CD18), Pgp-1 (CD44), CD45, MEL-14 (L-selectin), and VLA-4 alpha (CD49d), were all increased as a result of anti-CD2 treatment, whereas CD25 (IL-2R), CD48 (CD2 ligand), and ICAM-1 (CD54) remained unchanged. Kinetics showed that CD2 down-modulation was persistent and at the same magnitude from day 1 through day 7 of culture. Anti-CD2 mAb could down modulate CD2 on both CD4 and CD8 splenic lymphocyte subsets, thymocytes, and the T cell lymphoma EL-4; and, non-T cells did not seem to participate in the process of modulation. Mechanistic studies of mAb action showed that, in addition to 12-15, other anti-CD2 mAbs could cause down-modulation of T cell CD2 expression in an epitope and isotype dependent fashion and that CD2 down-modulation correlated with inhibition of receptor-driven T cell stimulation. Intact antibody, including the Fc portion, was required to induce CD2 down-modulation, and additional experiments suggested an interaction with an Fc gamma R other than Fc gamma RII or Fc gamma RIII. CD2 down-modulation did not change with the addition of the cytokines IL-1, IL-2, IL-6, IL-10, TNF alpha, or TGF-beta 1. These results show that anti-CD2 mAbs significantly and persistently down-modulate CD2 on various T cell subpopulations. The mAbs must interact with both the CD2 receptor and an Fc gamma R. CD2 down-modulation is accompanied by changes in the array of other T cell surface receptors that may contribute to mechanisms of anti-CD2-induced immunosuppression.

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